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Pre-pandemic early viral pneumonias; could we have encountered COVID-19 before? Accompanying a diagnostic model

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ABSTRACT

Aims: COVID-19 shows overlapping clinical and radiological findings with other viral pneumonias. This study designed to explore the likelihood of the existence of COVID-19 pneumonia in our country before March 11th, date of first official COVID-19 case detected in Turkey, by using a diagnostic model designed with radiologic and laboratory findings.

Methods: 273 patients with pre-diagnosis of viral pneumonia were aggrouped according to hospitalization date (before and after 11 March), naso-oropharyngeal swab PCR results. Thoracic tomographies, C-reactive protein (CRP), leukocyte, lymphocyte, monocyte, eosinophil, platelet values of all patients were evaluated.

Results: Laboratory findings of lymphocyte, eosinophil counts ($p<0.05$) were significantly low; radiologic findings of round opacity, cobblestone, nodüle, subpleural line were significant in COVID-19 group ($p<0.05$). 'Round opacity', 'subpleural line', 'nodule', 'lymphocyte' variables were found to be statistically significant for final model ($p<0.05$). COVID-19 diagnosis possibility; increases 302.9% by 'round opacity', 355.6% by 'subpleural lines'; and decreases 59.1% by 'nodule' presence, 31.7% by one unit increase in lymphocyte level. Based on final model; 49.3% of the participants before 11 March 2020 were predicted to be positive for COVID-19.

Conclusion: According to these findings, we can say that COVID-19 patients existed before March 11th, 2020 in Turkey, for the first time. Also based on same diagnostic model; subpleural lines, presence of cobblestone, round opacity appearances and absence of nodules on tomography, and the presence of lymphopenia and eosinopenia in the cell count can also be used to support the diagnosis of COVID pneumonia.

Keywords: COVID-19, pre-pandemic viral pneumonia, radiology findings, laboratory findings, diagnostic model

INTRODUCTION

Nowel coronavirus infection, which was introduced to the world on January 5th, 2020 by World Health Organization (WHO), became a global health problem towards the end of January and it was identified as coronavirus disease 19 (COVID-19) on the February 11th, 2020.[1] The first official COVID-19 case was detected on March 11th, 2020 in our country and this is the date which WHO announced the pandemic.[1,2] Since the first emergence of this pandemic; early diagnosis of the disease and quarantining the infected person have been accepted as the most important steps towards controlling the outbreak.[3,4] Although the definitive diagnosis is based on PCR positivity[5], due to the high false negativity and low sensitivity of this test, and the need for special laboratory conditions; some diagnostic models ranging from 'rule-based scoring systems' to 'advanced machine learning models' which evaluate clinical condition, comorbidities, symptoms, laboratory and radiological findings of the patient has been used to calculate the disease risk.[6,7]

Another reason for the difficulty in diagnosis is that COVID-19 shows similar clinical and radiological findings with other viral pneumonias, especially Influenza A (H1N1), occurring in the same periods as COVID every year.[8-12] Common symptoms related to COVID-19 infection like fever, cough, fatigue, dyspnea, myalgia and rarely sore throat, chest pain, runny nose, conjunctival congestion, nausea, vomiting, diarrhea can be seen.[13] In our clinical practice, since January 2020, we have noted that the number of cases with clinical and radiological findings of viral pneumonia, but pathological agents that could not be identified with PCR, has increased. Based on this prediction and as the first study on this subject; we aimed to explore the likelihood of

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the existence of COVID-19 pneumonia in our country before March 11th, 2020.

METHODS

The study was conducted with the permission of University of Health Sciences Samsun Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 30.06.2020, Decision No: 2020/10/5). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was designed retrospectively. We have included 120 patients who were hospitalized with clinically and radiologically proven viral pneumonia diagnosis and whose naso-oropharyngeal swab samples were taken between January 1st, 2020 and March 10th, 2020 and 168 patients who were diagnosed as COVID-19 and whose naso-oropharyngeal swab samples were taken between March 11th, 2020 and August 30th, 2020. Fifteen participants were excluded from the study because we could not reach their computerized tomography or laboratory findings.

In total, 273 patients were divided into two groups according to the date of March 11th, when the first COVID case has introduced in Turkey. Then these groups were categorized according to the PCR results (**Table 1**). Accordingly, group 1 included patients whose pathological agent were isolated in PCR testing before March 11th (n=36), group 2 patients whose pathological agent could not be identified in PCR testing before March 11th (n=79), group 3 included patients whose PCR tests were positive for COVID-19 after March 11th (n=83) and group 4 included patients whose PCR tests were negative for COVID-19 after March 11th (n=85) (**Table 1**).

Table 1. Study groups

All patients who have been included in the study (n=273)
1.Group: Pathological agent isolated with PCR before March 11th (n=36)
2.Group: Pathological agent couldn't be isolated with PCR before March 11th (n=69)
3.Group: Positive PCR result for COVID-19 after March 11th (n=83)
4.Group: Negative PCR result for COVID-19 after March 11th (n=85)

All scans were obtained using a 16-row multidetector scanner (Siemens Sensation 16, Erlangen, Germany) with the following parameters: 120 kVp, 150 mA, 1.5 mm collimation, 1.35:1 pitch, sharp kernel (B80f), reconstruction matrix of 512×512, slice thickness of 1.0 mm, and high spatial resolution algorithm.

Thoracic tomographies of all patients were independently evaluated by two different, blinded, 10-12 years experienced radiologists. Later, a council was held for the final report of the patients if there was no consensus. Each tomography was evaluated according to Fleischner society nomenclature and similar study recommendations.[15-17]

Tomographies were examined whether they have ground glass consolidation, distribution (peripheral, central, mixed), linear opacity, round opacity, cobblestone appearance, halo sign, tree-in-bud, interlobular septal thickening, bronchiectasis, cavitation, air bronchogram, nodule, subpleural line, lymphadenopathy, pleural thickening, pleural effusion and which lobe(s) involved (upper/middle/lower right and upper/lower left) (**Table 2**).

Table 2. Findings evaluated in tomographic scans

- Ground glass
- Consolidation
- Distribution (peripheral, central, mixed)
- Linear opacity
- Round opacity
- Cobblestone appearance
- Halo sign
- Tree-in-bud
- Interlobular septal thickening
- Bronchiectasis
- Cavitation
- Air bronchogram
- Nodule
- Subpleural line
- Lymphadenopathy
- Pleural thickening
- Pleural effusion
- Affected lobes (upper/middle/lower right and upper/lower left)

In all patients' blood tests; C-reactive protein (CRP), leukocyte, lymphocyte, monocyte, eosinophil, platelet values were included in the evaluations. We have also included neutrophil/lymphocyte, monocyte/lymphocyte, neutrophil/CRP, lymphocyte/CRP, eosinophil/CRP ratio evaluations during statistical analysis.

In the first stage, factors that differed significantly between COVID-19 groups (groups 3 and 4) were identified and logistic regression models were created by selecting these as independent variables. Based on the obtained predictive logistic regression model, the probability of having COVID-19 in patients with negative swab status before March 2020, namely group 2, was calculated. According to this probability, the possibility of encountering COVID-19 before March 11 was examined.

Statistical Analysis

In this study, we used the Fisher test for relations between categorical data and diagnosis of COVID-19 and an independent sample t-test for numerical measurements. Since the number of observations from COVID-19 diagnostic groups was n>30, a parametric method, t-test, was performed. Based on the obtained predictive logistic regression model, the probability of COVID-19 in the participant with a negative swap before March 2020 was calculated. Statistical analysis was performed using R-Project software (14) and IBM SPSS 22 program. Statistical test results were evaluated at a 95% confidence interval.

RESULTS

The median age of group 1 and 2 was 64.2, and the median age of group 3 and 4 was 54.8. Pathological agents isolated in the first group were; H1N1 (n=22), influenza B (n=2), rhinovirus (n=4), RSV A/B (n=3), corona NL63/HLU1 (n=3/1).

Laboratory Findings

Table 3 summarizes the results of the test hypothesis showing relations between laboratory findings including numerical measurements and COVID-19 diagnosis groups. According to test results, we found a statistically significant relation between COVID-19 groups and lymphocyte and eosinophil counts ($p<0.05$). Given the medians, patients who had a positive COVID-19 diagnosis had significantly lower lymphocyte and eosinophil levels.

Table 3. Statistical hypothesis test results for laboratory findings

Laboratory findings	COVID		p
	Positive (n=83)	Negative (n=85)	
Platelet	185 (95.1)	187 (134)	0.917
Neutrophil	41.5 (110)	70.5 (108)	0.129
Lymphoccyte	1.84 (1.45)	3.26 (3.01)	**0.001**
Monocyte	0.83 (0.96)	1.09 (0.90)	0.117
Eosinophil	0.18 (0.31)	0.34 (0.41)	**0.011**
C-reactive protein (CRP)	22.7 (31.1)	27.8 (64.1)	0.561
Neutrophil/lymphocyte	11.9 (25.2)	15.5 (21.6)	0.374
Monocyte/lymphocyte	0.57 (0.64)	0.45 (0.42)	0.221
Neutrophil/CRP	306 (886)	422 (810)	0.437
Lymphosite/CRP	5.13 (14.8)	12.0 (26.3)	0.063
Eosinophil/CRP	0.89 (2.47)	1.46 (2.79)	0.216

Data are represented as mean (standart deviation)

Radiological Findings

Table 4 shows the test hypothesis results of the relationships between the radiology findings including categorical data and the COVID-19 diagnosis groups. According to test results, we found a statistically significant relation between COVID-19 groups and cases with round opacity, cobblestone, nodule and subpleural line ($p<0.05$). Considering the percentages, the probability of having 'round opacity' and 'subpleural line' is higher in group 3 than in group 4. But the probability of having 'cobblestone' and 'nodule' is lower in group 3 in comparison to group 4.

Modelling

In **Table 5**, using the COVID-19 diagnostic groups as dependent variables a logistic regression model (full model) is created for the factors that are significant in the test hypothesis findings. Because 'eosinophil' and 'cobblestone' variables were found to be statistically insignificant a new model was developed by removing them from the model (final model). 'Round opacity', 'subpleural line', 'nodule' and 'lymphocyte' variables were found to be statistically significant in this model ($p<0.05$). According to the odds ratio, patients who had round opacity are 302.9% more likely to have a positive COVID-19 diagnosis than those who did not have it. Furthermore, we found that patients who had subpleural lines are 355.6% more likely to have a positive COVID-19 diagnosis. The presence of a nodüle decreases the likelihood of COVID-19 positivity by 59.1 percent. One unit increase in lymphocyte level causes a 31.7% decrease in the probability of a positive COVID-19 diagnosis.

Table 6 shows the performance metric results for the final logistic regression model. Based on these results, the accurate classification rate of the model established to predict the diagnosis of COVID-19 is 70.4%, the sensitivity is 68.3%, and the specificity is 72.5%. The Nagelkerke-R^2 value of the model is at the level of 31% and is far from zero. According to the performance metrics, the prediction performance of the model was found to be sufficient and all the parameters included in the model are significant. The C index value of the logistic regression model is 0.778 and the model's power to differentiate COVID-19 patients from healthy individuals is quite sufficient.

In this logistic regression model, we used 'round opacity', 'subpleural line', 'nodule' and 'lymphocyte' values of the participants before March 11th, 2020 as independent variables

Table 4. Statistical hypothesis test results for tomographic findings

Tomographic findings	COVID		p
	Positive (n=83)	Negative (n=85)	
Ground glass			
No	20.5%	20.0%	1.000
Yes	79.5%	80.0%	
Consolidation			
No	86.7%	76.5%	0.129
Yes	13.3%	23.5%	
Distribution			
Absent	16.9%	22.4%	
Peripheral	37.3%	21.2%	0.132
Central	2.41%	2.35%	
Mixed	43.4%	54.1%	
Linear opacity			
No	68.7%	81.2%	0.090
Yes	31.3%	18.8%	
Round opacity			
No	44.6%	74.1%	**<0.001**
Yes	55.4%	25.9%	
Cobblestone			
No	83.1%	97.6%	**0.003**
Yes	16.9%	2.35%	
Halo sign			
No	94.0%	91.8%	0.797
Yes	6.02%	8.24%	
Tree-in-bud			
No	96.4%	87.1%	0.056
Yes	3.61%	12.9%	
Bronchiectasis			
No	96.4%	87.1%	0.056
Yes	3.61%	12.9%	
Interseptal thickening			
No	81.9%	80.0%	0.903
Yes	18.1%	20.0%	
Cavitation			
No	100%	98.8%	1.000
Yes	0.00%	1.18%	
Air bronchogram			
No	83.1%	82.4%	1.000
Yes	16.9%	17.6%	
Nodule			
No	77.1%	54.1%	**0.003**
Yes	22.9%	45.9%	
Subplevral line			
No	66.3%	82.4%	**0.027**
Yes	33.7%	17.6%	
LAP			
No	91.6%	81.2%	0.083
Yes	8.43%	18.8%	
Pleural thickening			
No	89.2%	80.0%	0.153
Yes	10.8%	20.0%	
Pleural effusion			
No	96.4%	90.6%	0.228
Yes	3.61%	9.41%	
Right middle			
No	42.2%	38.8%	0.776
Yes	57.8%	61.2%	
Right lower			
No	27.7%	38.8%	0.173
Yes	72.3%	61.2%	
Right upper			
No	41.0%	38.8%	0.900
Yes	59.0%	61.2%	
Left upper			
No	37.3%	49.4%	0.155
Yes	62.7%	50.6%	
Left lower			
No	31.3%	44.7%	0.104
Yes	68.7%	55.3%	

Table 5. Logistic regression analysis results for COVID-19 diagnosis

Variable	Full model			Final model		
	Exp (β)	Wald	p	Exp (β)	Wald	p
(Intercept)	0.813	-0.467	0.640	0.690	-0.879	0.380
Round opacity (yes)	0.334	-2.643	**0.008**	0.330	-2.725	**0.006**
Cobblestone (yes)	0.205	-1.901	0.057	-	-	-
Subpleural line (yes)	0.288	-2.624	**0.009**	0.281	-2.693	**0.007**
Nodule (yes)	2.404	2.054	**0.040**	2.447	2.139	**0.032**
Lymphocyte	1.475	2.195	**0.028**	1.464	2.992	**0.003**
Eosinphil	0.818	-0.254	0.799	-	-	-

Exp (β): Odds ratio

Table 6. Performance metric results for the final logistic regression model

Metric	p
Accuracy	0.704
Sensitivity	0.683
Specificity	0.725
C index	0.778
Nagelkerke-R^2	0.310

and estimated rate of COVID-19 diagnoses. Based on this logistic regression model, 49.3% of the participants before 11 March 2020 were predicted to be positive for COVID-19. According to these findings, we can say that COVID-19 patients existed before March 11th, 2020 in Turkey.

DISCUSSION

The goal of this study was to investigate the unproven existence of COVID in the patients who were diagnosed with radiologically or clinically proven viral pneumonia but the pathological agent could not be identified before the announcement of the first COVID case in Turkey on January 1th, 2020. For this purpose, we used a model based on the radiological and laboratory values of 168 patients who have positive or negative COVID-19 PCR results and found that before the 11th of March the probability of COVID in the viral pneumonia patients whose agent could not be isolated was 49.3%. This is the first known probability assessment study for our country.

Due to the low sensitivity and high false negativity of the PCR, the suspicion of COVID infection is frequently investigated with CT findings. Fang et al.[18] reported that the sensitivity of the first PCR was 71%. Some studies indicated >90%[19] and 97%[17] sensitivity of CT scans for the diagnosis of this disease. There have been many publications on radiological features thought to be specific for COVID pneumonia. Nevertheless, ground-glass opacity is the most striking feature for both COVID and other viral pneumonias. In a meta-analysis of 2738 patients in 13 studies[20]; ground-glass opacities, interlobular septal thickening, adjacent pleural thickening and air bronchogram and especially bilateral and lower lobe localized lesions were found to be significant for COVID.

In another meta-analysis comparing COVID-19 confirmed by PCR with other viral pneumonia[21]; the findings specific to COVID were stated as predominantly ground-glass opacity, secondly mixed pattern including consolidation, and thirdly bilateral and mostly lower lobe involvement. However, in non-COVID cases, mainly a mixed pattern consisting of ground glass and consolidation, ground glass in the second and bilateral and lower lobe involvement in the third was detected. In another study comparing CT findings of COVID-19 and H1N1 infections by Yin at al.[22]; peripheral or peribronchovascular distribution, ground-glass opacity, consolidation, subpleural line, air bronchogram appearances did not show a statistically significant difference between the groups. Since the patients included in our study were hospitalized with suspicion of viral pneumonia, especially with a ground-glass appearance in their clinics and tomographies, and PCR samples were taken after hospitalization; ground-glass opacities and predominant involvement of any lobe were statistically significant in our patient group.

Wu at al.[23] categorized 130 patients whose COVID infection was confirmed by an antibody test according to radiological findings, first CT was taken in 1-20 days after the onset of symptoms and control CT's were taken in 3-27 days. They mentioned three different distribution according to this categorization. Lobular distribution; is the most common form in which the virus settles in the center of the lobule and rapidly spreads to the environment creating a ground-glass pattern. Diffuse distribution; is the form in which both lobule and subpleural space are involved. Subpleural distribution; starts from blood vessel and lymphatics rich interstitium of the lobules located in subpleural areas and causes a more serious inflammatory response. If the virus spreads through the interlobular especially perialveolar interstitium, lymphatic drainage of this area is either towards the interseptal area or subpleural area. Since it cannot extend distally in the subpleural area, progression is observed parallel to the pleura, which causes subpleural lines. Wu at al.[23] mentioned that this appearance is characteristic for the novel coronavirus pneumonia but is not specific as it can also be seen in other viral pneumonias. In our study, however, subpleural streaking was detected as a specific finding for COVID-19 infection (p=0.007) and was used in the final model. In the same study again, as in severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), it has been referred that 'cobblestone appearance' is an important marker of interlobular septum involvement, but it is nonspecific for other viral pneumonias. In our study, the incidence of 'cobblestone appearance' was lower in the COVID-19 positive group than in the negative group.

Wu et al.[23] examined the follow-up CT images of 35 patients; they interpreted regression of ground-glass opacity, consolidation, corner contraction and retractions, subpleural line or fiber strips and bronchiectasis as changes due to

organization. It has been stated that consolidation was more frequent in the late phases of COVID and the patient group above 50 years of age.[24] Interlobular septal thickening may indicate the presence of interstitial fluid, cell infiltration or fibrosis, as well as parainfluenza, hantavirus and SARS infections.[25] In our COVID-19 positive patient group, consolidation and interseptal thickening were not statistically significant.

While comparing CT findings of COVID-19 and *Influenza pneumonia*[26]; it has been mentioned that the presence of peripherally distributed round opacities and interlobular septal thickening and the absence of nodule and tree-in-bud appearance can be used to differentiate COVID-19 from influenza pneumonia. The size of the nodule can give an idea about the differential diagnosis of infectious causes and it has been previously reported that lesions below 1 cm may have a viral origin.[27] In the study of Pan et al.[24], while nodules were seen in 71% of the influenza infections, they were observed in only 28% of the COVID-19 infections. Also, Liu et al.[26] reported that a combination of some CT findings may be useful in differentiating COVID and influenza. These findings are listed as the presence of pure ground-glass/round opacity/interlobular septal thickening and absence of nodules; the presence of pure ground-glass and inter-lobular septal thickening; the presence of round opacity and interlobular septal thickening; and absence of pleural effusion. In our study, we have found that round opacity and subpleural line increased the possibility of having COVID by 302.9% and 355.6% respectively. Also, the presence of nodules decreased the possibility of having a positive diagnosis for COVID-19 by 59.1%. These three findings were used in modelling by providing sufficient reliability in logistic regression analysis (C index=0.078).

Studies have been conducted not only on radiologic findings but also on practical laboratory tests that can be used in the differential diagnosis when the patient presents with the first symptom. In a study designed fort his goal by Lia at al.[28], it has been reported that decreased leukocytes (<9.5 10^9/L), lymphopenia (<1.1 10^9/L), eosinopenia (<0.02 10^9/L), increased CRP (>4 mg/dl) were associated with COVID, particularly combination of eosinopenia and CRP elevation has 67.9% sensitivity and 78.2% specificity in terms of disease diagnosis.

Eosinopenia is seen in 50-70% of severe COVID patients. The underlying cause is uncertain, but there are some predictions. These are; decreased eosinophilopoiesis, defect in eosinophil release from bone marrow, increased eosinophil apoptosis due to IFN-1 released during acute infection.[29] The event of eosinophils binding to the virus and inactivating the virus[30], which has been shown in influenza A and respiratory syncytial virus (RSV) infections, may also be valid in COVID infections. Similar to eosinopenia, lymphopenia has also been found to be an independent risk factor for mortality in COVID.[31] Conditions causing lymphopenia can be listed as T-cell burnout, increase in lymphocyte proptosis and apoptosis, decrease in bone marrow suppression and release during cytokine storm.[32] In our study; eosinophils and lymphocytes were found to be significantly lower in COVID-19 patients, and they were found suitable for use only in the lymphopenia diagnosis model after logistic regression. In our study, eosinophils and lymphocytes were significantly lower in COVID-19 patients, and after logistic regression, they were only found suitable for use in the lymphopenia diagnosis model.

In the final model, we found that round opacity, subpleural line, nodule and lymphocyte were statistically significant. This model was used for the 2nd group (patients whose agent could not be isolated before March 11th) and the probability of COVID-19 was calculated as 49.3% (n=34). In a review examining models created for diagnosis, prognosis and mortality risk[6], such models were approached with bias and their routine use was not recommended because of not selecting control patients appropriately, exaggerated positive and sometimes suspicious results, and it was thought that they were entered the academic literature very quickly and there was an optimistic approach regarding their performance in cases where there was an urgent need for medical support. The goal of using a model in our study was to predict the probability in our previous patients and build this prediction on robust statistical data.

There are various publications that this novel type of coronavirus was found in nature before December 2019, and that causes disease. In their study, Forstera et al.[33] follow the phylogenetic network of the SARS-CoV-2 genome and after examining more than 10.000 phylogenetic studies of various organisms, they concluded that the final version of the virus that caused the infection emerged before December 24, 2019. Also, SARS-CoV-2 RNA was found in a water sample from November in Brazil.[34] Additionally, the COVID-19 antibody was detected in blood samples taken between December 2019 and January 2020 in the United States.[35]

Limitations

Our study has several limitations. First, only 273 patients were included. Larger studies might support these results. Second limitation was that samples from the pre-COVID period could not be serologically examined. However, with the high reliability of our statistical findings, our results support the possibility of this virus started to cause infection before the announced introduction date in our country.

CONCLUSION

Radiologic and laboratory findings can be useful in the early prediction and differentiation of COVID pneumonia and other viral pneumonias before the PCR results are obtained. Subpleural lines, presence of cobblestone, round opacity appearances and absence of nodules on tomography, and the presence of lymphopenia and eosinopenia in the cell count can also be used to support the diagnosis of COVID pneumonia.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of University of Health Sciences Samsun Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 30.06.2020, Decision No: 2020/10/5).

Informed Consent
Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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